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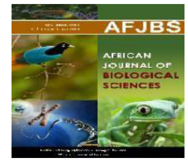

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The Effect of Magnesium Replacement Therapy in Altering the Course of Hypocalcaemia Post Total Thyroidectomy in Thyroid Cancer Patients

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Abstract: Purpose:Despite routine supplementation of calcium and vitamin D pre- and post-thyroidectomy, there is a high percentage of persistently hypocalcaemic patients. There is also a trend of low magnesium levels post thyroidectomy, the magnitude of is greater, in patients developing hypocalcaemia suggesting a strong relationship between magnesium levels and hypocalcaemia.

Methods:Eligible patients (n =78) undergoing total thyroidectomy for thyroid cancer were randomly assigned to receive oral supplements of 1,500 mg/day elemental calcium, 1 mcg/day alfacalcidol with or without 340 mg elemental magnesium for 2 weeks.. Serum ionized calcium levels and symptoms of hypocalcaemia were followed for 28 days as well as serum magnesium levels.

Results:The percentage of symptomatic hypocalcaemia was higher in the control group without statistical significance (p value=0.525). The Mg level was significantly different between groups at days 7 and 14 postoperative only but there was no significant difference in the ionized calcium levels at days 1, 2, 3, 7, 14 and 28 between both groups. The mean ionized Ca^{2+} of the study group at day 28 post -operative was statistically significantly lower than at day 14 post-operative.

Conclusion:Magnesium replacement therapy resulted in a non-significant reduction in the incidence and duration of symptomatic hypocalcaemia post total thyroidectomy..

Keywords: Thyroid cancer, Magnesium Replacement Therapy, Hypocalcaemia, Hypothyroidism and Total thyroidectomy

Introduction

The incidence of thyroid cancer has risen dramatically over the past four decades, with similar patterns observed internationally (Kitahara CM and Schneider AB, 2022). Because surgery is the mainstay of treatment for thyroid cancer, there is a growing interest in reducing postoperative complications (Callender GG et al., 2014). Postoperative transient hypocalcaemia is the most frequent complication after thyroidectomy, with a reported incidence of 1.6%–50% (Bergenfelz A et al., 2008)despite normalparathyroid hormone levels. Postoperative hypocalcaemia is associated with longer hospital stay, the need for extra blood tests, and increased medical costs (Yoon JH, 2011). Several studies investigated preventive measures to reduce postoperative hypocalcaemia, including postoperative supplementation of calcium (Ca), vitamin D, and/or thiazide diuretics (Antakia R et al., 2015). Routine calcium and vitamin D supplementation has been most widely used, especially in outpatient thyroidectomy patients, to decrease the risk of symptomatic hypocalcaemia after thyroidectomy (Terris DJ et al., 2013). However, there is still a high percentage of persistent hypocalcaemia despite calcium and vitamin D supplementation (Docimo et al., 2012). Despite being one of the major issues post total thyroidectomy, the causes of hypocalcaemia are not totally clear until now (Del Rio et al., 2019). Many factors have been extensively investigated as a risk factor of hypocalcaemia. One of these factors is hypomagnesaemia. Magnesium (Mg) is the second most abundant intracellular divalent cation, which is important for many biologic and cellular functions. Hypomagnesaemia has been associated with hypocalcaemia in chronic disease states, because it could lead to impaired parathyroid hormone (PTH) secretion and end-organ resistance to PTH which together contribute to the development of hypocalcaemia (R.K. Rude et al., 1976; R. Garty et al., 1983 and S. Mori et al., 1992). In addition, hypomagnesaemia shares the same symptoms with hypocalcaemia. Thus, postoperative hypomagnesaemia may increase both the biochemical and symptomatic hypocalcaemia incidence in patients undergoing total thyroidectomy (TT) (A. Sousa Ade et al., 2010). The present study investigated the effect of routine magnesium replacement therapy on both hypomagnesaemia and hypocalcaemia post total thyroidectomy.

METHODS

Study design

This study was a prospective randomized, open-labelled, controlled trial conducted at The Egyptian National Cancer Institute between August 2021 and August 2022. The Research Ethics Committee at the Faculty of Pharmacy at Cairo University approved the study by the number **CL (3147)**. This study was also registered at the Pan African Clinical Trial Registry (pactr.samrc.ac.za) database. (**PACTR202401789967358.**)

Eligible patients were randomly assigned into two groups with a 1:1 allocation using a table of random numbers generated from random.org website to receive calcium and vitamin D with magnesium supplementation (study group) or calcium and vitamin D without magnesium supplementation (control group). A written informed consent was obtained from each participant.

Patient selection

Patients were included in the study if they were 18-65 years of age, had a diagnosis of thyroid carcinoma and underwent bilateral total thyroidectomy, normal parathyroid levels and post-operative hypocalcaemia, defined as an ionized calcium concentration below 4.6 mg/dl (normal range, 4.6–5.4 mg/dl). Patients with suspicious lymph node on ultrasound underwent therapeutic lymph node (LN) dissection. Eligibility also included normal renal function (Scr ≤ 1.3 mg/dl), normal hepatic function (ALT ≤ 55 U/L & AST ≤ 48 U/L) and normal preoperative serum calcium (8.6: 10.3 mg/dl), ionized calcium (4.65: 5.25 mg/dl), magnesium (1.6: 2.6 mg/dl), phosphorus (2.6: 4.5 mg/dl) and vitamin D (20: 50 ng/mL) levels.

Pregnant women, cognitively impaired or mentally disabled subjects, patients with history of thyroid surgeries and patients with other types of cancer other than thyroid cancer were excluded. Patients were also excluded if no parathyroid glands were preserved, intravenous calcium or magnesium supplementation were used to treat severe symptomatic hypocalcaemia or hypomagnesaemia and in case of prior use of any medication that would affect calcium levels.

Procedures

The demographic and baseline characteristics including: age, sex and BMI were collected and Ionized Ca level, Mg level, P level, vitamin D level, Scr level, albumin level, ALT level and AST level, parathyroid hormone level were measured one day before surgery. All patients received regular post total thyroidectomy treatment (Ca supplements (1500 mg equivalent of calcium daily) and vitamin D supplement (1 mcg alfacalcidol daily) for 28 days). The patients started 1.5mcg/kg levothyroxine post-operatively and they were allowed to eat normal amounts of food containing calcium and magnesium with no restrictions on the dietary calcium intake. The study group patients were assigned to oral magnesium citrate 2125 mg daily which gives approximately 340 mg elemental magnesium (Epimag® effervescent powder/ 1 sachet daily) in case of normal magnesium levels post-operative and 4250 mg daily divided into two doses which gives approximately 680 mg elemental magnesium (Epimag ® effervescent powder/ 2 sachets daily) in case of mild hypomagnesaemia post-operatively (Mg level > 1.2 mg/dl) till the magnesium level is normalized then the normal daily need dose was continued till the end of 14 days post-operative period knowing that the magnesium replacement therapy dosing is based on the daily need of elemental magnesium which is 320 – 420 mg/day. The control group patients were assigned to the regular post total thyroidectomy treatment (Ca supplements (1500 mg equivalent of calcium daily) and vitamin D supplement (1 mcg alfacalcidol daily) for 28 days) with no oral magnesium supplementation. The blood samples were withdrawn one day before surgery to confirm eligibility for inclusion in the study and at the morning of the days 1, 2, 3, 7, 14 and 28 post-operatively to be analyzed at the National Cancer Institute Laboratory. Follow-up tests included clinical evaluation for hypocalcaemia. The clinical assessment was done through face-to-face interview with the patient during which the patient was asked close-ended questions in Arabic language; about each symptom of hypocalcaemia and was given discrete choices to pick one of them. A validated checklist in Arabic was developed for this purpose.

Study end points

The primary endpoint of the study was to investigate the effect of magnesium replacement therapy on hypocalcaemia and hypomagnesaemia post total thyroidectomy by two measures; the first measure is the comparison between the ionized calcium levels and magnesium levels of the study group and the control group at two-weeks and 28 days post-operative and the second measure is the difference in time taken to relieve the symptoms of hypocalcaemia between the study and control groups.

The secondary endpoint of this study was to assess the prevalence of symptomatic hypocalcaemia post total thyroidectomy. This is expressed as the percentage of patients that experienced symptomatic hypocalcaemiaduring 28 days post total thyroidectomy.

Statistical analysis

Sample size of this study was calculated using GPower_3.1.9.4 for continuous parametric data for two independent study groups with alpha = 0.05, power = 80% and enrolment ratio 1: 1. The anticipated mean of calcium levels post thyroidectomy for group 1 was 9.4 ± 0.9 which is expected after using magnesium(F. Turgut et al., 2008) and group 2 = 8.9 ± 0.5(Ghafouri A et al., 2014).The result was a total of 54 subjects for the two groups (Rosner B, 2011).To avoid loss of statistical power due to patient drop-out an additional 10% of patients were recruited, thus the sample size was more than 30 patients per group.

Statistical tests were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Continuous variables were compared using Mixed- ANOVA and Independent T test and categorical variables were compared using Chi-Square test. Two-sided P-values ≤0.05 were considered statistically significant.

RESULTS

From Aug 2021 to Aug 2022, 117 patients with thyroid cancer underwent total thyroidectomy in our institution. Nine patients were older than 65 years and 4 patients were younger than 18 years. Five patients had no preserved parathyroid glands. Seven patients were excluded due to preoperative hypocalcaemia and nine due to preoperative vitamin D deficiency. Four patients had renal impairment and only one patient suffered from hepatic impairment. The remaining 78 patients were randomly assigned 1:1 after total thyroidectomy, whether to receive or not to receive magnesium supplementation with routine calcium and vit D supplementation as shown in figure 1. After randomization, six patients in the study group showed no postoperative hypocalcaemia (n= 5) or severe symptomatic hypocalcaemia which was treated by intravenous calcium supplementation (n= 1) and were further excluded from the analysis. Eight patients in the control group were also excluded due to absence of postoperative hypocalcaemia (n= 5), severe symptomatic hypocalcaemia which was treated by intravenous calcium supplementation (n= 2) and patient death (n= 1). The sudden death of the patient who died at day 16 post-operative and was excluded from the control group during the study was attributable to a postsurgical complication. Thirty three patients in the study group and 31 patients in the control group were included for the final analysis. The mean age of the study group was 41 years (± 10.45) and of the control group was 44 years (±11.83). The percentage of males all over the study was 17% only and it was 18% and 16% of the study and control groups respectively. Sixty-four percent of the subjects retained their full parathyroid glands (4 preserved parathyroid glands) 22 subjects of the study group and 19 subjects of the control group. Thirty-six percent had ≤3 preserved parathyroid glands 11 subjects of the study group and 12 subjects of the control group (33% had 3 preserved parathyroid glands, 3% had 2 preserved parathyroid glands). Fourteen subjects of the study group and 7 subjects of the control group had neck dissection combined with their surgery. According to the inclusion criteria the subjects with vitamin D deficiency were excluded and the mean of vitamin D levels were 27ng/ml with 95% of the patients between 19.6 and 37.4 ng/ml. About 67.2%of the 64 subjects of this study developed symptoms of hypocalcaemia. The percentage of symptomatic hypocalcaemia was higher in the control group compared to the study group (71% and 63.6% respectively) with no statistical significance (p value=0.525). The symptoms were categorized into mild moderate and severe, 5 patients of the study group and 5 patients of the control group showed mild symptoms in the form of irritability and weakness, 8 patients of the study group and 13 patients of the control group developed moderate symptoms as paresthesia, and 8 patients of the study group and 4 patients of the control group suffered from severe symptoms such as cramps and tetany. The majority of the patients (95%) experienced these symptoms within 3 days postoperative. Twelve of the symptomatic subjects started manifestations at day 1 postoperative, 14 at day 2, 15 at day 3, 1 at day 7 and 1 at day 28. The mean duration of symptoms was 1.65 days (SD=1.14) in the study group and 1.91 days (SD=1.15) in the control group with no significant difference (p value=0.468). Mg levels were significantly different between the study group and the control group at days 7 and 14 postoperative only. The null hypothesis was accepted for the ionized calcium levels at days 1, 2, 3, 7, 14 and 28 between the study group and the control group. The mean of ionized Ca^{2+} of the study group was 4.47 mg/dl (SD=0.408) at day 14 and 4.38 mg/dl (SD=0.419) at day 28 (p value = 0.048). The mean Mg level of the study group was 2.18 mg/dl (SD=0.0334) on day 14 and 1.9 mg/dl (SD=0.0434) on day 28 (p value = 0.000).

The clinical baseline characteristics of the 64 included patients are shown in Table 1 and the outcomes are demonstrated in Table 2.

The differences of the means of ionized calcium levels and magnesium levels between the study and the control groups are demonstrated in Figure.2 and Figure.3 respectively.

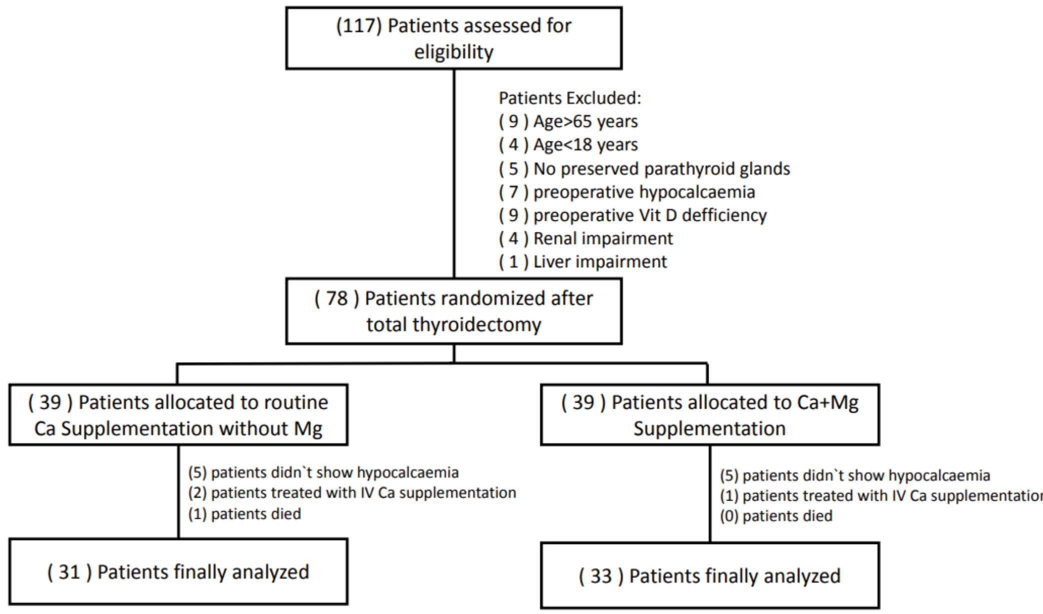

Figure.1.Patient Enrollment Flow chart

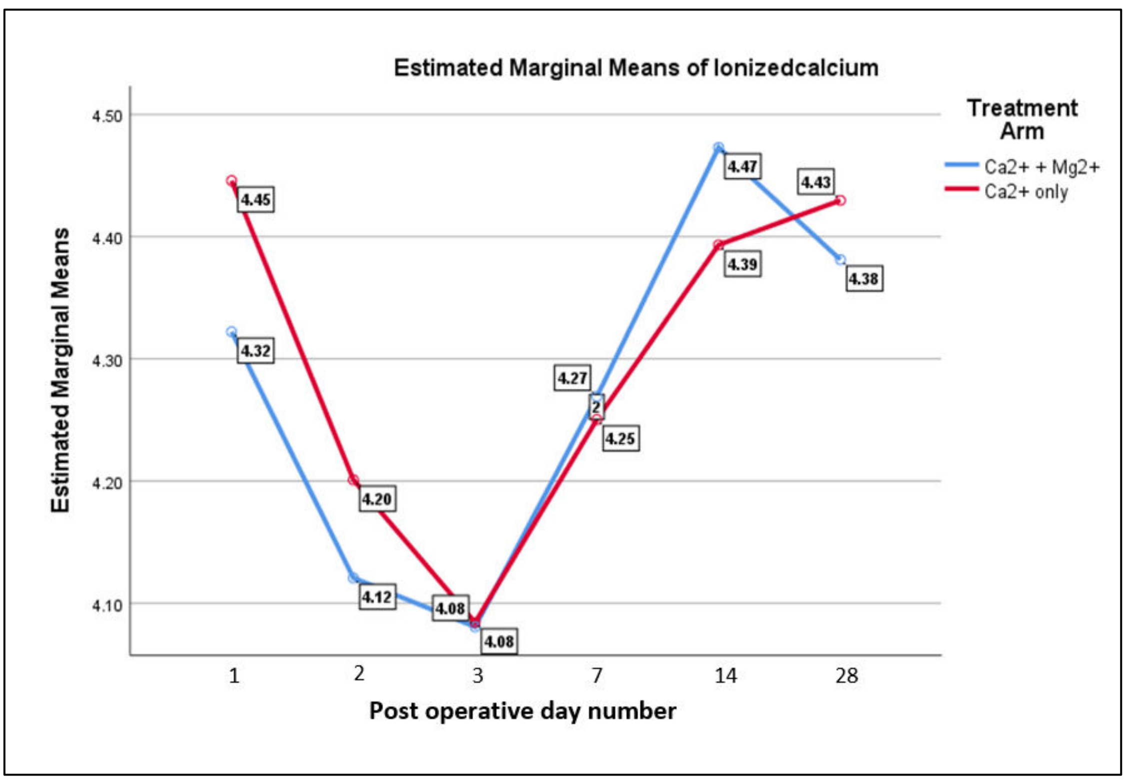

Figure 2. Comparison of the means of ionized calcium levels between the study group and the control group using Mixed- ANOVA statistical analysis (p-value is 0.303)

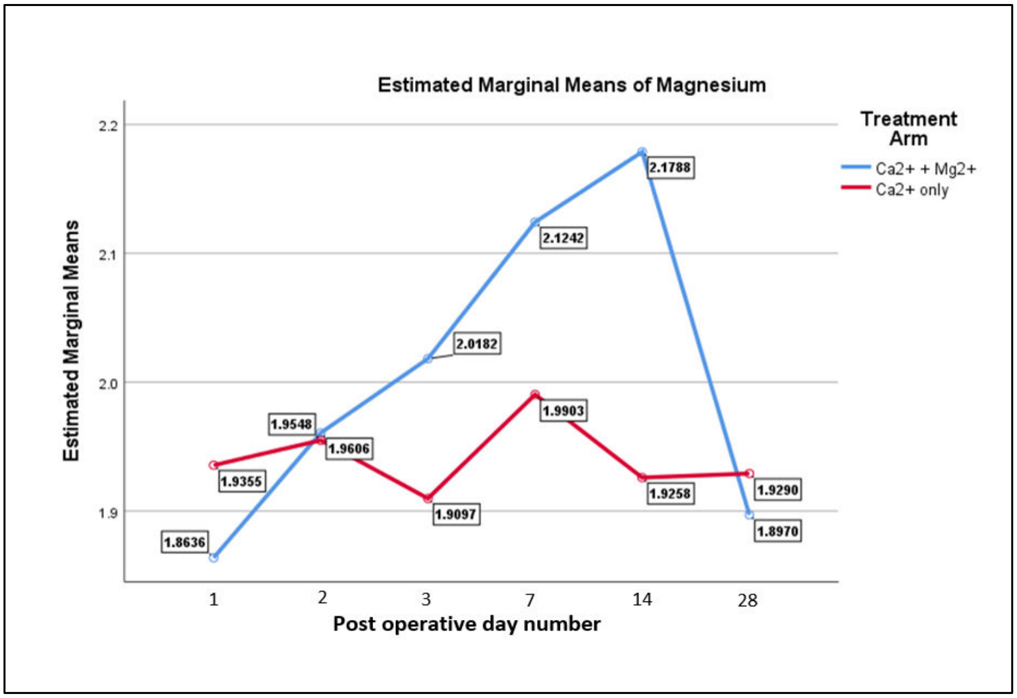

Figure 3. Comparison of the means of magnesium levels between the study group and the control group using Mixed- ANOVA statistical analysis (p-value is <0.001)

Table.1 Demographic and baseline characteristics of the study patients.

Characteristics	Study Group (n=33)	Control Group (n=31)	P Value
Sex			
Female: n (%)	27 (81.8%)	26 (83.9%)	0.828
Age mean (SD)	41.03 (10.45)	44.03 (11.83)	0.285
BMI* mean (SD)	24.173 (2.95)	25.881 (4.41)	0.072
Ionized Ca* mean (SD)	4.6885 (0.318)	4.7732 (0.33)	0.3
Mg* mean (SD)	1.921 (0.193)	2.013 (0.309)	0.157
P* mean (SD)	3.812 (0.63)	3.829 (0.603)	0.913
Vitamin D mean (SD)	27.467 (4.01)	26.506 (4.845)	0.39
Scr.* mean (SD)	0.827 (0.172)	0.839 (0.212)	0.813
ALT mean (SD)	18.03 (9.15)	20.9 (8.54)	0.2
AST mean (SD)	23.55 (10.2)	26.1 (11.45)	0.35
Combined LN* dissection	14 (42.4%)	7 (22.6%)	0.091
No. of preserved PTG*			
2	1 (3.0%)	1 (3.2%)	0.903
3	10 (30.3%)	11 (35.5%)	
4	22 (66.7%)	19 (61.3%)	

Values are presented as number (%) or mean ± standard deviation.
**BMI: Body mass index, Ca: Calcium, Mg: Magnesium, P: Phosphorus, Scr.: Serum creatinine level, LN: Lymph node, PTG: Para thyroid gland.*
▲*Independent T test was used to compare continuous variables and Chi-Square test was used to compare categorical variables*

Table.2. Primary and secondary study outcomes

Characteristics	Magnesium Supplement Group (n=33)	Control Group (n=31)	P Value
Symptoms			
No symptoms (%)	12	9	0.525
Irritability (%)	0	1	
Weakness (%)	5	4	
Paresthesia (%)	8	13	
Cramps(%)	5	3	
Tetany (%)	3	1	
Mean of Duration of symptoms (SD)	1.65 (1.14)	1.91 (1.15)	0.468
Mean of Days Of Hospitalization (SD)	4.58 (1.15)	4.58 (1.09)	0.986
Laboratory Findings			
Mean of D*1 Ionized Ca* (SD)	4.3221 (0.42)	4.4458 (0.34)	0.2
Mean of D1 Ionized Mg* (SD)	1.864 (0.22)	1.935 (0.31)	0.29
Mean of D2 Ionized Ca* (SD)	4.1206 (0.46)	4.2010 (0.29)	0.4
Mean of D2 Ionized Mg* (SD)	1.961 (0.26)	1.955 (0.32)	0.936
Mean of D3 Ionized Ca* (SD)	4.0806 (0.41)	4.0842 (0.3)	0.968
Mean of D3 Ionized Mg* (SD)	2.018 (0.25)	1.910 (0.32)	0.135
Mean of D7 Ionized Ca* (SD)	4.2691 (0.37)	4.2503 (0.33)	0.83
Mean of D7 Ionized Mg* (SD)	2.124 (0.21)	1.990 (0.28)	0.034
Mean of D14 Ionized Ca* (SD)	4.4730 (0.41)	4.3932 (0.36)	0.41
Mean of D14 Ionized Mg* (SD)	2.179 (0.19)	1.926 (0.27)	0.000
Mean of D28 Ionized Ca* (SD)	4.3812 (0.42)	4.4297 (0.39)	0.634
Mean of D28 Ionized Mg* (SD)	1.897 (0.25)	1.929 (0.24)	0.6

Values are presented as number (%) or mean ± standard deviation

**D: Day, Ca: Calcium, Mg: Magnesium*

▲ *Mixed Anova and Independent T test were used to compare continuous variables and Chi-Square test was used to compare categorical variables*

DISCUSSION

Despite oral calcium and vitamin D administration both before and after total thyroidectomy, there is still a high percentage of persistent hypocalcaemia. A study by G.Docimo et al in 2012 showed that around 18% of patients undergoing total thyroidectomy suffered from post-operative hypocalcaemia (6% had symptomatic hypocalcaemia and 2% required I.V calcium for critical symptoms) even with using appropriate dose of calcium and vitamin D pre and post-surgery (Docimo et al., 2012). It was also clear in the study by Lee et al. that routine low-dose calcium supplementation did not reduce the risk of postoperative hypocalcaemia as the incidence of symptomatic hypocalcaemia showed no difference between the calcium group (low dose calcium supplementation and vitamin D) and control group(Lee JW et al., 2019).

It is well known that postoperative hypocalcaemia is the most common complication after total thyroidectomy, which may be asymptomatic or symptomatic. The critical period for monitoring serum calcium post thyroidectomy is (24 to 96 hours) after surgery (Del Rio et al., 2019). Our study showed that symptoms of hypocalcaemia appear mainly in the first three days postoperative.

Although it is very common, the cause and the mechanism of hypocalcaemia following thyroidectomy remains inconclusive (Garrahy A et al., 2016).There is little data regarding the impact of hypomagnesaemia and the effect of magnesium (Mg) replacement therapy on the development of hypocalcaemia after total thyroidectomy in literature especially in thyroid cancer patients undergoing total thyroidectomy.

Hypomagnesaemia on day 1 post-operative after thyroidectomy was significantly associated with hypocalcaemia (Del Rio et al., 2019). There is a downward trend in magnesium levels in patients after total thyroidectomy which persists through the second postoperative day, with the magnitude of fall in magnesium levels being greater in patients developing biochemical hypocalcaemia (Brophy C et al., 2019). This was also observed in the present study as there was a downward trend in magnesium levels post-operatively in the control group and there was a significant difference in Mg levels at days 7 and 14 post-operative between the study group and the control group. Although the drop of Mg levels at day 28 post-operative in the study group after stopping magnesium supplementation wasn`t below the clinically acceptable threshold, it demonstrates the role of Mg supplementation in maintaining normal Mg levels through the first two weeks postoperative.

Most of the previous publications on the association of magnesium levels with post-thyroidectomy measured magnesium levels at numerous time points, but the time points of the index magnesium level used for predicting hypocalcaemia are not clear (Wilson RB et al., 2000 and Cherian AJ et al., 2016).

Only one previous paper has examined trends in magnesium levels after thyroidectomy. Sousa et al reported a significant drop in magnesium levels between preoperative values and day 1 post-operative among both patients developing and not developing hypocalcaemia. Hypocalcaemic patients also showed a significant drop in magnesium levels on day 2 post-operative from preoperative values; however, this drop was not significant among patients not developing hypocalcaemia. In that study, there was no analysis performed for association between hypomagnesaemia and hypocalcaemia, or correlation between magnesium and calcium levels (A. Sousa Ade et al., 2010). Although the mean of ionized calcium levels was slightly higher in the treatment group without a significant difference in our study, the statistically significant decrease between the ionized calcium levels at day 14 and day 28 demonstrates the significant effect of magnesium supplementation on calcium levels. The percentage of symptomatic patients with hypocalcaemia which was higher in the control group compared to the study group and the mean duration of symptoms that was lower in the study group than in the control group, although statistically non-significant, shows a trend of decrease in symptoms and duration with magnesium supplementation.

One of the limitations of the current study is that the variations in the normal eating and drinking habits of the subjects after surgery may have an impact on magnesium, calcium and other electrolyte levels. Another limitation was the time of hospitalization post-operative was during the COVID-19 epidemic and the fast track surgery policy was implemented in our health system for all patients undergoing total thyroidectomy, therefore all patients were hospitalized for the same period postoperatively.

CONCLUSION

Magnesium replacement therapy have clearly treated the downward trend in magnesium levels even within the normal range values in patients after total thyroidectomy which is accompanied by a non-statistically significant decrease in symptomatic hypocalcaemia as shown by the lower percentage of symptomatic subjects and shorter duration of symptoms. Our study does not provide a strong evidence of the effect of magnesium replacement therapy on the ionized calcium levels post thyroidectomy. The drop of the mean ionized calcium levels after stopping magnesium supplementation between day 14 post-operative and day 28 post-operative in the study group may indirectly illustrate the magnesium supplementation effect. Further data are required to confirm the effect of aggressive treatment of hypomagnesaemia on hypocalcaemic patients after thyroidectomy.

RECOMMENDATION

According to the results of this study we recommend to give Mg supplementation with the dose of 340 mg elemental Mg/day routinely post total thyroidectomy for patients with hypocalcaemia and hypomagnesaemia as Mg supplementation is conducive to reducing the occurrence of symptoms of hypocalcaemia and correcting the downward trend in magnesium levels.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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